REMARKS

Upon entry of this amendment, claims 70-94 are pending in the instant application. Claims 1, 3-8, 13-20 and 22 have been cancelled herein, without prejudice or disclaimer. Claims 2, 9-12, 21, and 23-69 were previously cancelled. Applicants reserve the right to prosecute the cancelled subject matter, as well as the originally presented claims, in continuing applications. Support for new claims 70-94 is found in the specification, figures, and claims as filed, and at least at pages 11-22, page 25, and pages 36-37. Accordingly, no new matter is added.

I. RCE

The Examiner has indicated that amendment and response filed on 4/12/04 has been fully considered and entered into the application.

II. Information Disclosure Statement

The Examiner has indicated that the listing of references in the specification is not a proper information disclosure statement, and that unless the references are cited on form PTO-892, they will not be considered by the Examiner. Applicants submit that a proper information disclosure statement will be filed at a later date.

III. Specification

The Examiner has objected to the specification at page 37, lines 13-14 for referring to claim 1. Applicants submit that this paragraph was amended in the Preliminary Amendment filed with the RCE submission mailed on April 8, 2004 (See page 2 of the Preliminary Amendment). As the Examiner has indicated that this Preliminary Amendment has been fully considered and entered, all references to claim 1 have already been deleted from the specification. Accordingly, Applicants request that this objection be withdrawn.

IV. § 112, First Paragraph Rejection: Written Description

The Examiner has rejected claims 1, 3-8, 13-20, and 22 under 35 U.S.C. § 112 first paragraph for lack of written description, contending that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In response, Applicants note that claims 1, 3-8, 13-20, and 22 have been canceled herein. Therefore, this rejection is moot as it pertains to these claims. The various aspects of the written description rejection as to the extent that they apply to the claims as emended are addressed below.

Marsilje Article

The Examiner has indicated that the specification disclosure is based on the methods taught by a reference publication (Marsilje, 2000), which was published after the filing date of the instant application, and that the article is required to practice the claimed invention. *See* Office Action at page 4.

Applicants respectfully disagree. Even though the specification makes reference to the Marsilje article (Marsilje *et al.*, Bioorganic & Medicinal Chemistry Lett. 10 (2000) 477-481) at pages 24 and 50, the teachings of the article are presented as Example 1 in the instant application. For example, Table 1 of the Marsilje article, at page 478, is identical to Table 6 of the instant application (p. 42); Scheme 1 of the Marsilje article, at page 478, is identical to Scheme 1 of the instant application (p. 40); and Scheme 2 of the Marsilje article, at page 478, is identical to Scheme 2 of the instant application (p. 43). Furthermore, many of the paragraphs of the Marsilje article are presented throughout the specification of the instant application. Therefore, Applicants submit that the Marsilje article is not required to practice the claimed invention, as the teachings of this article are actually present in the application itself. Furthermore, provisional application USSN 60/115,643, the priority document for the instant application, contains an almost identical version of the text of the Marsilje article, and is incorporated by reference in the instant specification. See USSN 60/115,643, pages 1-6. Therefore, Applicants request that this rejection be withdrawn.

Descriptive Method

The Examiner has indicated that the specification discloses a descriptive method (in-silico or hypothetical method) based on computer modeling of the kinases in identifying protein kinase inhibitors. *See* Office Action at page 4. Applicants respectfully disagree. The invention relates to a rational method of identifying inhibitors of a protein kinase using an iterative procedure of steps involving a *combination* of structure-based design (*e.g.*, using molecular modeling), chemical synthesis and *in vitro* assay techniques. See, *e.g.*, Figure 1; page 6, line 23-

page 7, line 16; page 9, lines 6 and 27-31; and the Declaration of David G. Hangauer, Jr., under 37 C.F.R. § 1.132 submitted herewith.

Furthermore, new independent claim 70 relates to a method of identifying a kinase inhibitor based on the inhibitory activity of a compound in a kinase assay. Dependent claims 89-91 relate to the use of molecular modeling techniques to assist in designing a kinase inhibitor, *which is then tested* to determine kinase inhibition capability.

Functional Characteristics

The Examiner has indicated that the first module of the claims is defined only by functional characteristics of the compounds (*i.e.*, capable of binding to catalytic residues of a protein kinase), which are not considered to be distinguishing characteristics to show that the Applicants are in possession of the invention. *See* Office Action at page 5. Applicants respectfully disagree.

The as-claimed invention relates to a method of identifying an inhibitor of a protein kinase by providing a first reagent that includes a peptide scaffold (a protein kinase substrate) covalently linked to one of a specifically enumerated set of first modules; testing the first reagent for kinase inhibition, selecting a first reagent that has kinase inhibition activity, based on the results of the kinase inhibition assay, and using this information to provide a second reagent that includes the first module from the first reagent that has kinase inhibition activity covalently linked to a second module that is one of a specifically enumerated group of non-protein scaffolds; testing the second reagent for kinase inhibition, and selecting a second reagent that has kinase inhibition activity, based on the results of the kinase inhibition assay. *See, e.g.*, Figure 1; page 6, line 23-page 7, line 16; page 9, lines 6 and 27-31; and the Declaration of David G. Hangauer, Jr., under 37 C.F.R. § 1.132 submitted herewith. Applicants submit that the first module of the pending claims is not "only defined by the functional characteristics of the compounds" and that this rejection should be withdrawn.

Producing Inhibitor Compounds

The Examiner has also indicated that the specification does not disclose how the inhibitor compounds are produced. *See* Office Action at page 5. Applicants respectfully disagree. There is ample disclosure on how to synthesize first compounds including a peptide scaffold covalently linked to a first module. *See*, for example, Figure 1; Table 1; Table 2; Table 3; page 36, lines 3-4 and 8-13; and Example 1.

Additionally, there is ample disclosure on how to synthesize second compounds including a non-peptide scaffold (second module) covalently linked to a first module. See, for example, Figure 1; Figure 6; Figure 7; Figure 8; Table 4; page 4, lines 24-26; page 7, lines 25-28; page 36, lines 6-7 and 14-20; and Examples 1, 2, 3, and 4.

Finally, there is ample disclosure on how to synthesize third compounds including a non-peptide scaffold (second module) covalently linked to a first module and to specificity elements. See, for example, Figure 1; Figure 9; Table 5; page 34, lines 5-32; page 36, lines 30-33; and Examples 1, 2, 3, and 4.

First Module Having Functional Groups

The Examiner has also indicated that the "specification description does not sufficiently teach the first module having functional groups". Office Action at page 5. As amended herein, the pending claims do not relate to a first module having functional groups. As such, the rejection is moot and should be withdrawn.

Open Ended Claim

The Examiner has also indicated that the "specification description clearly does not provide adequate representation regarding the open-ended method of the instant claim". Office Action at page 6. Applicants respectfully request clarification of this aspect of the rejection. However, Applicants believe that the claims, as amended herein, are not open ended, and, moreover, these claims are sufficiently described in such a way as to convey to a person of ordinary skill in the art that Applicants had possession of the claimed invention. As such, the rejection is moot and should be withdrawn.

Guidance

The Examiner has also indicated that the "specification disclosure does give sufficient guidance on how to identify the first module which have functional groups which can bind to a catalytic sites of a protein kinase". Office Action at pages 6-7. Further, the Examiner states that "[t]he specification does not sufficiently teach the structure of the first module such that the starting reagents in the claimed method are known. The specification does not give any guidance on selecting the first module or how to identify the first module having functional groups capable of binding to a protein kinase conserved catalytic sites or which compounds are used as first module." Applicants respectfully disagree.

First, the claims as amended herein, do not require one to identify the first module that has functional groups which can bind to the catalytic core of a protein kinase. Specifically, the claimed method relates to a method of identifying an inhibitor of a protein kinase by providing a first reagent that includes a peptide scaffold (a protein kinase substrate) covalently linked to one of a specifically enumerated set of first modules; testing the first reagent for kinase inhibition, selecting a first reagent that has kinase inhibition activity, based on the results of the kinase inhibition assay, and using this information to provide a second reagent that includes the first module from the first reagent that has kinase inhibition activity covalently linked to a second module that is one of a specifically enumerated group of non-protein scaffolds; testing the second reagent for kinase inhibition, and selecting a second reagent that has kinase inhibition activity, based on the results of the kinase inhibition assay. *See, e.g.*, Figure 1; page 6, line 23-page 7, line 16; page 9, lines 6 and 27-31; and the Declaration of David G. Hangauer, Jr., under 37 C.F.R. § 1.132 submitted herewith.

Second, in the newly presented claims, the "identifying" step comprises measuring the ability of a first, second, or third reagent to inhibit phosphorylation activity relative to a control reaction, the "identifying" does not relate to "covalently attaching a first module to a scaffold".

Third, Applicant submits that the specification does indeed provide guidance on selecting the first module, based on the ability of the first reagent to inhibit kinase phosphorylation activity. In claim 70, the first module is specifically selected from boronic acid, a hydroxyl group, phosphonic acid, sulfamic acid, a guanidino group, a carboxylic acid, an aldehyde, an amide, and hydroxymethylphosphonic acid. Such first modules are listed, for example, on page 36, lines 8-13 of the specification. See also, Table 2.

Thus, the invention relates to a *rational* method of identifying inhibitors of a protein kinase using an iterative procedure of steps involving a *combination* of structure-based design (*e.g.*, using molecular modeling), chemical synthesis and *in vitro* assay techniques. See, *e.g.*, Figure 1; page 6, line 23-page 7, line 16; page 9, lines 6 and 27-31; and the Declaration of David G. Hangauer, Jr., under 37 C.F.R. § 1.132 submitted herewith.

Furthermore, new independent claim 70 relates to a method of identifying a kinase inhibitor based on the inhibitory activity of a compound in a kinase assay. Dependent claims 89-91 relate to the use of molecular modeling techniques to assist in designing a kinase inhibitor,

which is then tested to determine kinase inhibition capability. Assay conditions are described, *e.g.*, at page 13, lines 10-25 and in Examples 1 and 2.

In light of the newly presented claims, and the above remarks, Applicants respectfully request that the § 112 first paragraph, written description, rejection be withdrawn.

V. § 112, First Paragraph Rejection: Enablement

The Examiner has rejected claims 1, 3-8, 13-20, and 22 under 35 U.S.C. § 112 first paragraph for lack of written description. She contends that the specification, "while enabling for indole or naphthalene as the non-peptide scaffold, and the use of specific functional groups as the first module (M1 in Table 1), does not reasonably provide enablement for the broad scope of the instantly claimed method" Office Action at page 8. In response, Applicants note that claims 1, 3-8, 13-20, and 22 have been canceled herein. Therefore, this rejection is moot as it pertains to these claims. The various aspects of the enablement rejection to the extent they apply to the claims as amended herein are addressed below.

As presently claimed, the first module is specifically selected from boronic acid, a hydroxyl group, phosphonic acid, sulfamic acid, a guanidino group, a carboxylic acid, an aldehyde, an amide, and hydroxymethylphosphonic acid. Such first modules are listed, for example, on page 36, lines 8-13 of the specification. Applicants submit that several compounds have been synthesized containing the various first module groups. See, for example, Tables 1-5, and the Hangauer Declaration, for example at paragraphs 8, 10, and 11.

Under 35 U.S.C. § 112, first paragraph, lack of enablement is found only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See, United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Even if the experimentation required is complex, it is not necessarily undue if artisans skilled in the relevant art typically engage in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm. 1983).

The factors used to determine whether experimentation is undue include, but are not limited to the following: (1) the breadth of the claims; (2) the nature of the invention; (3) the amount of direction provided by the inventor; (4) the existence of working examples; (5) the level of predictability in the art; (6) the state of the prior art; (7) the level of one of ordinary skill

in the art; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See In re Wands*, 858 F.2d at 737. No one of these factors is dispositive and the Examiner must consider the evidence as a whole. *Id.*; M.P.E.P. § 2104.01(a). Here, the declarant has stated that it is his view that the claimed invention is enabled and that the ordinarily skilled artisan would be able to routinely use the described methods of identifying a kinase inhibitor. *See* Hangauer declaration.

Moreover, in order to make an enablement rejection, the Examiner has the burden to establish a reasonable basis to question the enablement for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); M.P.E.P § 2164.04. In view of the evidence and arguments submitted herewith, the Examiner cannot meet this burden -- and the Examiner has not provided any evidence or factual support that would establish such basis for the rejection.

Applicants note that the specification provides an extraordinary amount of direction concerning how to practice the claimed invention. The declarant unequivocally concurs that the specification provides ample guidance to the ordinarily skilled artisan -- *see* Hangauer Declaration, *e.g.*, paragraphs 4, 7, 14.

By way of example, the instant specification teaches and discloses the types of first and second modules which are used in the methods of the invention. (*See* page 36, lines 3-20). Applicants have provided several working examples of kinase inhibitors identified according to the method of the invention. (*See* Specification, Examples 1-2; Tables 4-6).

a) Guidance

The Examiner indicated that the specification fails to give adequate direction or guidance as to the means of identifying at least on functional group on the first module, or how to identify a first module, or the chemical structure of the first module (except for the pentapeptide scaffold). *See* Office Action at page 9.

The first paragraph of § 112 requires that, to enable a claimed invention, an application must describe "how to use" the invention. In response to this rejection, Applicants point out that methods for carrying out the claimed invention are described throughout the specification. Specifically, the claimed method relates to a method of identifying an inhibitor of a protein kinase by providing a first reagent that includes a peptide scaffold (a protein kinase substrate) covalently linked to one of a specifically enumerated set of first modules; testing the first reagent for kinase inhibition, selecting a first reagent that has kinase inhibition activity, based on the

results of the kinase inhibition assay, and using this information to provide a second reagent that includes the first module from the first reagent that has kinase inhibition activity covalently linked to a second module that is one of a specifically enumerated group of non-protein scaffolds; testing the second reagent for kinase inhibition, and selecting a second reagent that has kinase inhibition activity, based on the results of the kinase inhibition assay. *See, e.g.*, Figure 1; page 6, line 23-page 7, line 16; page 9, lines 6 and 27-31. Methods of identifying a kinase inhibitor based on the inhibitory activity of a compound in a kinase assay are described, *e.g.*, at page 13, lines 10-25 and in Examples 1 and 2.

Moreover, as Dr. Hangauer explicitly states in his declaration, there is ample guidance in the specification about how to perform the method of the invention. *See*, for example, paragraphs 7-14.

Applicants have made a significant contribution to the art by discovering a rational method of discovering small molecule inhibitors of protein kinases using both *in silico* design AND *in vitro* assay procedures. The non-peptide inhibitors identified by this method have minimal structural complexity, such that the structure of the inhibitors are only as complex as needed to achieve the desired biological objectives, but not more; they have good oral drug properties relative to peptide inhibitors. The method allows efficient screening of large numbers of compounds and produces a much higher percentage of active compounds relative to random or maximum diversity combinatorial library design. *See* Appendix B of the Hangauer declaration, presenting kinase inhibition data from a combinatorial library that shows high "hit rates", meaning that the percent of the library that are good kinase inhibitors is higher than that in a random library, when assayed against three different kinases and one phosphatase. The "hit rate" for a random or maximum diversity library is typically much less that 1%. In this library the hit rate (meaning inhibition equal or greater than 10% at 10 micromolar) for all four targets was much higher than that. In this table, a blank cell means the % inhibition was less than 10%.

Applicants submit that a person of ordinary skill in the art, with the specification in hand and given the state of the art at the time of filing, could make and use the claimed methods of identifying an inhibitor of a protein kinase.

Thus, because applicants have provided an enabling description of "how to use" the claimed invention, the "how to use" requirement of § 112 has been satisfied and this rejection should be withdrawn.

b) Scope

The Examiner indicated that the specification working examples are drawn to specific compounds with either naphthalene or indole scaffold compounds as protein kinase inhibitors, and that the specification does not provide an enabling disclosure of the full scope of the claimed invention. *See* Office Action at pages 9-10. Applicants disagree.

As presently claimed, the second module, non-protein scaffold is selected from indole, naphthalene, biphenyl, isoquinoline, benzofuran, and benzothiophene. *See* page 36, lines 14-20. Specific compounds for each of these scaffolds were synthesized and tested. *See*, for example, Table 4. *See* also, page 26, line 1 and Example 2 for discussion of indole compounds; Tables 5 for and Example 1 for discussion of naphthalene compounds; page 26, line 11-17 for a discussion of biphenyl compounds; page 26, line 1 for a discussion of isoquinoline compounds; page 25, line 30 for a discussion of benzofuran compounds; and page 25, line 1 for a discussion of benzothiophene compounds. *See* also the Hangauer Declaration.

c) Utility

The Examiner indicated that "the specification disclosure only speculates the utility of the resulting compounds as protein kinase inhibitors." Office Action at page 10.

Applicants disagree. As claimed, the method of identifying a kinase inhibitor involves testing the compounds for the ability to inhibit the phosphorylation reaction of the kinase. There is ample teaching as to the methods of assaying enzyme activity under literature mimetic conditions, as well as under the cellular mimetic conditions developed by the Applicants. *See, e.g.*, page 13, lines 10-25 and Examples 1 and 2. The utility of a kinase inhibitor is to inhibit a kinase.

Furthermore, the ability of inhibitors identified by the method of the invention to inhibit growth of cancer cell lines. This activity was also compared to that of known anticancer agents. *See* Example 5, and in Figures 14 and 15. Thus, the method of the invention is useful to identify compounds useful to treat cancer.

d) State of the Art

The Examiner indicated that "the state of the prior art at the time the invention was made is such that protein kinase inhibitors are specific to the kinases and in general are known to be difficult resulting in non-functional compounds" Office Action at page 10.

As presented herein, the claims relate to a method of identifying an inhibitor of a protein kinase by providing a first reagent that includes a peptide scaffold (a protein kinase substrate) covalently linked to one of a specifically enumerated set of first modules; testing the first reagent for kinase inhibition, selecting a first reagent that has kinase inhibition activity, based on the results of the kinase inhibition assay, and using this information to provide a second reagent that includes the first module from the first reagent that has kinase inhibition activity covalently linked to a second module that is one of a specifically enumerated group of non-protein scaffolds; testing the second reagent for kinase inhibition, and selecting a second reagent that has kinase inhibition activity, based on the results of the kinase inhibition assay. *See, e.g.*, Figure 1; page 6, line 23-page 7, line 16; page 9, lines 6 and 27-31. Methods of identifying a kinase inhibitor based on the inhibitory activity of a compound in a kinase assay are described, *e.g.*, at page 13, lines 10-25 and in Examples 1 and 2. Thus, by definition, the method of the invention identifies compounds that are functional- *i.e.*, that are active in inhibiting the kinase phosphorylation reaction. See also, Hangauer declaration, paragraphs 8 and 9 for a discussion of choosing pentapeptide scaffolds for designing the first reagents useful in the claimed method.

e) Unpredictability

The Examiner indicated that "the art is unpredictable because organic synthesis (or modifications) and screening for active compounds is unpredictable when applied to compounds of diversity." Office Action, page 10.

Applicants have discovered a rational method of discovering small molecule inhibitors of protein kinases using both *in silico* design AND *in vitro* assay procedures. The non-peptide inhibitors identified by this method have minimal structural complexity, such that the structure of the inhibitors are only as complex as needed to achieve the desired biological objectives, but not more; they have good oral drug properties relative to peptide inhibitors. The method allows efficient screening of large numbers of compounds and produces a much higher percentage of active compounds relative to random or maximum diversity combinatorial library design. See Appendix B of the Hangauer declaration, presenting kinase inhibition data from a combinatorial library that shows high "hit rates", meaning that the percent of the library that are good kinase inhibitors is higher than that in a random library, when assayed against three different kinases and one phosphatase. The "hit rate" for a random or maximum diversity library is typically much less that 1%. In this library the hit rate (meaning inhibition equal or greater than 10% at 10

micromolar) for all four targets was much higher than that. In this table, a blank cell means the % inhibition was less than 10%. As such, the practice of the invention, *i.e.*, rationally screening for a kinase inhibitor is not unpredictable relative to the methods currently used in the screening art.

For all the foregoing reasons, the rejection should be withdrawn -- the pending claims are enabled.

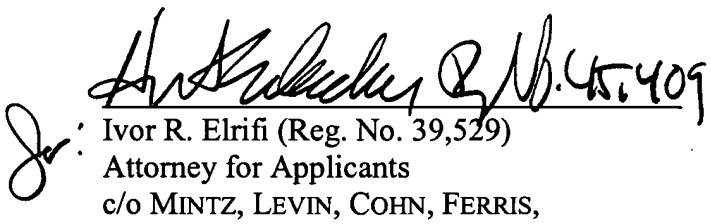
VI. Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3-8, 13-20, and 22 are rejected under 35 U.S.C. §112, second paragraph as being indefinite, and for omitting essential structural cooperative relationships of elements. Claims 1, 3-8, 13-20, and 22 are cancelled herein, rendering this rejection moot. As such, Applicants respectfully request that the Examiner withdraw this rejection.

CONCLUSION

On the basis of the foregoing, Applicants respectfully request that the rejection of the pending claims be withdrawn. If there are any questions regarding these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



Ivor R. Elrifi (Reg. No. 39,529)
Attorney for Applicants
c/o MINTZ, LEVIN, COHN, FERRIS,
GLOVSKY AND POPEO, P.C.
Telephone: (617) 542-6000
Customer No. 30623